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10/644,052

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/644,052	<b>Applicant(s)</b> KRIEG ET AL.	
	<b>Examiner</b> Nina A. Archie	<b>Art Unit</b> 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 03 October 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-5, 12-17, 22-28, 32, 36, 39, 44, 46, 48-49, 66-67, 70, 88, 94-100 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 12, 14, 16, 17, 22, 24, 26, 27, 49, 66, 67, 97, 98 and 100 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 3, 2008 has been entered.

### ***Amendment Entry***

2. The amendment filed October 3, 2008 has been entered. Claims 1-5, 12-17, 22-28, 32, 36, 39, 44, 46, 48-49, 66-67, 70, 88, 94-100 are pending. Claims 3-5, 13, 15, 23, 25, 28, 32, 36, 39, 46, 48, 70, 88, and 94-99 are withdrawn. Claims 6-11, 18-21, 29-31, 33-35, 37-38, 40-43, 45, 47, 50-65, 68-69, 71-87, and 89-93 are cancelled.

### ***Double Patenting Rejection Maintained***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claim 49 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Application No. 11/361,313 is maintained is maintained for the reason set forth in the previous office action.

Examiner accepts Applicant's remarks that respectfully requests that this rejection be held in abeyance since the co-pending claim has not yet been allowed. Applicant notes that the instant claims have an earlier priority date. If in fact a double patenting rejection is appropriate, which applicant does not agree with, the earlier filed claims should be allowed and the rejection should be made in the later filed application.

***Claim Rejection Maintained - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. The rejection of claims 1-2, 12, 14, 16-17, 22, 24, 26-27, 44, 49, 66-67, 97-98, and 100 under 35 U.S.C. 102(b) as being anticipated by Krieg et al WO/01/22972A2.

**Applicant arguments:**

The Examiner contended that the cited publication teaches each and every feature of the instantly claimed invention. This contention is respectfully traversed for the reasons presented below. Contrary to the Examiner's assertion, the WO/01/22972 A2 by Krieg et al. does not anticipate the instant claims because the cited reference

Art Unit: 1645

does not teach each and every element of the claimed invention. The cited reference merely teaches that an immunostimulatory oligonucleotide may include a chimeric backbone, e.g., a backbone comprising phosphodiester in part and phosphorothioate in part. The cited reference does not specifically teach that the phosphodiester linkage be placed at a specified position. In addition to this generic limitation, however, the instant claims require a further limitation. The instant claims specify that "at least one internal YZ dinucleotide has a phosphodiester or phosphodiester-like internucleotide linkage." Thus, not only the oligonucleotide of the claimed invention comprises a chimeric backbone, but also it is required to have a phosphodiester or phosphodiester-like linkage at the specified position (i.e., at least one internal YZ dinucleotide).

This is based on the discovery, which was first recognized by Applicant, as disclosed in the instant application, that having a phosphodiester internucleotide linkage at the YZ dinucleotide position (e.g., between C\_G), not only did not adversely affect the immunostimulatory activity of the oligonucleotides but in some cases resulted in enhanced immunostimulatory activity. This was a surprising finding and was counterintuitive, because it was known in the art that a phosphodiester linkage is more susceptible to nuclease-mediated degradation, and therefore, having a phosphodiester linkage at the CpG dinucleotide motif would be expected to result in the breakage of the oligonucleotide at the site, destroying the immunostimulatory motif. Nevertheless, it was discovered that placing a phosphodiester between the C and the G in an otherwise phosphorothioate-modified oligonucleotide did not result in a loss of immunostimulatory activity. Based at least in part on this finding, the instant invention is drawn to an immunostimulatory nucleic acid molecule having at least one internal pyrimidine-purine (YZ) dinucleotide and a chimeric backbone, wherein the at least one internal Y-Z dinucleotide has a phosphodiester or phosphodiester-like internucleotide linkage.

Applicant fails to find the teaching of a YZ motif having a phosphodiester or phosphodiester like linkage in the cited reference. Rather, the oligonucleotides of the cited reference represent a genus of immunostimulatory oligonucleotides that encompasses the species of oligonucleotides provided in the instant disclosure. Applicant respectfully submits that the case law is clear in that a prior art reference that

Art Unit: 1645

teaches a genus does not anticipate all species of a later claimed invention. See, for example, *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category." Thus, because the cited reference does not teach every limitation of the instant claims, *prima facie* case of anticipation has not been established. Applicant respectfully submits that the instantly claimed invention is novel.

### **Examiner's Response to Arguments**

Examiner accepts Applicant's argument. However Examiner disagrees, the prior art reference teaches the limitations of the claims. The claimed invention is drawn to an immunostimulatory nucleic acid molecule having at least one internal pyrimidine-purine (YZ) dinucleotide and a chimeric backbone, wherein the at least one internal YZ dinucleotide has a phosphodiester or phosphodiester-like internucleotide linkage, wherein optionally each additional internal YZ dinucleotide has a phosphodiester, phosphodiester-like, or stabilized internucleotide linkage, and wherein all other internucleotide linkages are stabilized.

Therefore, Krieg et al (prior art reference is referred to whenever Krieg et al is stated in the Argument) teach, immunostimulatory oligonucleotides which have chimeric backbones and which do not require the presence of a CpG motif. However Krieg et al teach that the invention in one aspect relates to a composition of an oligonucleotide having a formula: 5'Y<sub>1</sub>N<sub>1</sub>ZNZY<sub>2</sub> 3', wherein Y<sub>1</sub> and Y<sub>2</sub> are, independent of one another, nucleic acid molecules having between 1 and 10 nucleotides, wherein Y<sub>1</sub> includes at least one modified internucleotide linkage and Y<sub>2</sub> includes at least one modified internucleotide linkage and wherein N<sub>1</sub> and N<sub>2</sub> are nucleic acid molecules, each independent of one another, having between 0 and 5 nucleotides, but wherein N<sub>1</sub>ZN<sub>2</sub> has at least 6 nucleotides in total and wherein the nucleotides of ZN<sub>2</sub> have a phosphodiester backbone, wherein Z is a nucleic acid sequence selected from the group consisting of TTTT, TG, and a sequence wherein at least 50% of the bases of the sequence are Ts. Krieg et al teaches that in some embodiments Y<sub>1</sub> and/or Y<sub>2</sub> have

Art Unit: 1645

between 3 and 8 nucleotides. In other embodiments Y1 and/or Y2 are comprised of at least three Gs, at least four Gs, least seven Gs, or all Gs. In other embodiments Y and/or Y2 are selected from the group consisting of TCGTCG, TCGTCGT, and TCGTCGTT (SEQ ID NO : 1145). In yet other embodiments Y1 and/or Y2 include at least one, two, three, four, or five poly-A, poly-T, or poly-C sequences. Krieg et al further teach that center nucleotides (N1ZN2) of the formula Y1N1ZN2Y2 have phosphodiester internucleotide linkages and Y1 and Y2 have at least one modified internucleotide linkage. In some embodiments Y1 and/or Y2 have at least two modified internucleotide linkages. In other embodiments Y1 and/or Y2 have between two and five modified internucleotide linkages. In yet other embodiments Y1 has two modified internucleotide linkages and Y2 has five modified internucleotide linkages or Y1 has five modified internucleotide linkages and Y2 has two modified internucleotide linkages. The modified internucleotide linkage, in some embodiments is a phosphorothioate modified linkage or phosphorodithioate modified linkage. Krieg et al teaches a composition of a sustained release device including an immunostimulatory oligonucleotide having the formula Y1N1ZN2Y2, is provided according to another aspect of the invention (see abstract, pgs. 2-12, pgs. 18-24, pgs. 27-30, pg. 34, pgs. 36-37).

Krieg et al teach that the invention also includes nutritional supplements of an immunostimulatory oligonucleotide having the formula Y1N1ZN2Y2, in a delivery device. Krieg et al further teach that in another aspect the compositions described above also include an immunostimulatory nucleic acid having an unmethylated CG dinucleotide, a TG dinucleotide or a Py-rich sequence wherein the immunostimulatory nucleic acid having an unmethylated CG dinucleotide, a TG dinucleotide or a Py-rich sequence has a different sequence than the oligonucleotide comprising 5'Y, N, ZN2Y2 3'.

Krieg et al teach that in some embodiments the immunostimulatory nucleic acid having an unmethylated CG dinucleotide, a TG dinucleotide or a Py-rich sequence has a completely phosphodiester backbone and in other embodiments the immunostimulatory nucleic acid having an unmethylated CG dinucleotide, a TG dinucleotide or a Py-rich sequence has a modified backbone, which optionally may have

Art Unit: 1645

internucleotide linkages selected from the group consisting of phosphorothioate, phosphorodithioate, and p-ethoxy.

Krieg et al teach that in one embodiment immunostimulatory nucleic acid having an unmethylated CG dinucleotide has a formula comprising: 5'X<sub>1</sub>X<sub>2</sub>CGX<sub>3</sub>X<sub>4</sub> 3' wherein X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub> and X<sub>4</sub> are nucleotides. In other embodiments the immunostimulatory nucleic acid sequence includes at least the following formula: 5'TCNTXIX<sub>2</sub>CGX<sub>3</sub>X<sub>4</sub> 3' wherein N is a nucleic acid sequence composed of from about 0-25 nucleotides, wherein at least one nucleotide has a modified internucleotide linkage, and wherein the nucleic acid has less than or equal to 100 nucleotides. According to some embodiments XIX<sub>2</sub> are nucleotides selected from the group consisting of : GT, GG, GA and AA and X<sub>3</sub>X<sub>4</sub> are nucleotides selected from the group consisting of : TT, CT or GT. In a preferred embodiment X<sub>1</sub>; X<sub>2</sub> are GA and X<sub>3</sub>X<sub>4</sub> are TT. Furthermore the SEQ ID NO. 313 was elected in the restriction on 8/2/2006. Krieg et al teach SEQ ID NO. 313 (see abstract, pgs. 2-12, pgs. 18-24, pgs. 27-30, pg. 34, pgs. 36-37) and (STIC Sequence Search Results SEQ ID NO: 331). Therefore claims 66, 97, 98, and 100 are examined however only elected SEQ ID NO: 313 is searched thus species of claims 66, 97, and 98 are examined without SEQ. Furthermore Krieg et al teach claims 66, 97, and 98 and the limitations have been met. (see abstract, pgs. 2-12, pgs. 18-24, pgs. 27-30, pg. 34, pgs. 36-37).

Overall, Krieg et al teach Y<sub>2</sub> are selected from the group consisting of TCGTCG, TCGTCGT, and TCGTCGTT (SEQ ID NO : 1145). Krieg et al further Y<sub>1</sub>N<sub>1</sub>ZN<sub>2</sub>Y<sub>2</sub> have phosphodiester internucleotide linkages Y<sub>2</sub> have at least one modified internucleotide linkage and in some embodiments Y<sub>2</sub> has at least two-five modified internucleotide linkages.

Therefore the limitations have been met and maintained for the reason set forth in the previous office action.

As outlined previously, the instant claims are to draw an immunostimulatory nucleic acid molecule having at least one internal pyrimidine-purine (YZ) dinucleotide and a chimeric backbone, wherein the at least one internal YZ dinucleotide has a



Art Unit: 1645

phosphodiester or phosphodiester-like internucleotide linkage, wherein optionally each additional internal YZ dinucleotide has a phosphodiester, phosphodiester-like, or stabilized internucleotide linkage, and wherein all other internucleotide linkages are stabilized (claim 1); an oligonucleotide comprising an octameric sequence comprising at least one YZ dinucleotide having a phosphodiester or phosphodiester-like internucleotide linkage, and at least 4 T nucleotides, wherein Y is a pyrimidine or modified pyrimidine, wherein Z is a guanosine or modified guanosine, and wherein the oligonucleotide includes at least one stabilized internucleotide linkage (claim 49); an oligonucleotide comprising 5'GNC 3', wherein N is a nucleic acid sequence of 4-10 nucleotides in length and is at least 50% T and does not include a CG dinucleotide, and the oligonucleotide includes at least one stabilized internucleotide linkage (claim 67); an oligonucleotide comprising  $N_1$ -C\_G- $N_2$ -C\_G- $N_3$  wherein  $N_1$  and  $N_3$  are each independently a nucleic acid sequence 1-20 nucleotides in length, wherein \_ indicates an internal phosphodiester or phosphodiester-like internucleotide linkage, wherein  $N_2$  is independently a nucleic acid sequence 4-20 nucleotides in length, and wherein G- $N_2$ -C includes at least 5 stabilized linkages (claim 97); an oligonucleotide comprising  $N_1$ -C\_G- $N_2$ -C\_G- $N_3$  wherein  $N_1$ ,  $N_2$ , and  $N_3$  are each independently a nucleic acid sequence of 0-20 nucleotides in length and wherein \_ indicates an internal phosphodiester or phosphodiester-like internucleotide linkage, wherein the oligonucleotide is not an antisense oligonucleotide, triple-helix-forming oligonucleotide, or ribozyme (claim 98).

Krieg et al teaches an immunostimulatory nucleic acid molecule having at least one internal pyrimidine-purine (YZ) dinucleotide and a chimeric backbone, wherein the at least one internal YZ dinucleotide has a phosphodiester or phosphodiester-like internucleotide linkage, wherein optionally each additional internal YZ dinucleotide has a phosphodiester, phosphodiester-like, or stabilized internucleotide linkage, and wherein all other internucleotide linkages are stabilized, wherein the immunostimulatory nucleic acid comprises a plurality of internal YG dinucleotides having a phosphodiester or phosphodiester-like internucleotide linkage, wherein the at least one internal YG dinucleotide having a phosphodiester or phosphodiester-like internucleotide linkage is

Art Unit: 1645

CG, wherein the immunostimulatory nucleic acid molecule is a B-Class immunostimulatory nucleic acid molecule, wherein the immunostimulatory nucleic acid molecule is 4-100 nucleotides long, wherein the immunostimulatory nucleic acid molecule is not an antisense oligonucleotide, triple-helix-forming oligonucleotide, or ribozyme, wherein the nucleic acid has a backbone comprising deoxyribose or ribose, wherein the phosphodiester or phosphodiester-like internucleotide linkage is phosphodiester, wherein the stabilized internucleotide linkages are selected from the group consisting of: phosphorothioate, phosphorodithioate, methylphosphonate, methylphosphorothioate, and any combination thereof, wherein the stabilized internucleotide linkages are phosphorothioate (see abstract, pgs. 2-12, pgs. 18-24, pgs. 27-30, pg. 34, pgs. 36-37).

Krieg et al teaches an oligonucleotide comprising an octameric sequence comprising at least one YZ dinucleotide having a phosphodiester or phosphodiester-like internucleotide linkage, and at least 4 T nucleotides, wherein Y is a pyrimidine or modified pyrimidine, wherein Z is a guanosine or modified guanosine, and wherein the oligonucleotide includes at least one stabilized internucleotide linkage. Krieg et al teaches an oligonucleotide comprising 5'GNC 3', wherein N is a nucleic acid sequence of 4-10 nucleotides in length and is at least 50% T and does not include a CG dinucleotide, and the oligonucleotide includes at least one stabilized internucleotide linkage. Krieg et al teaches an oligonucleotide comprising  $N_1-C\_G-N_2-C\_G-N_3$  wherein  $N_1$  and  $N_3$  are each independently a nucleic acid sequence 1-20 nucleotides in length, wherein  $\_$  indicates an internal phosphodiester or phosphodiester-like internucleotide linkage, wherein  $N_2$  is independently a nucleic acid sequence 4-20 nucleotides in length, and wherein  $G-N_2-C$  includes at least 5 stabilized linkages. Krieg et al teaches an oligonucleotide comprising  $N_1-C\_G-N_2-C\_G-N_3$  wherein  $N_1$ ,  $N_2$ , and  $N_3$  are each independently a nucleic acid sequence of 0-20 nucleotides in length and wherein  $\_$  indicates an internal phosphodiester or phosphodiester-like internucleotide linkage, wherein the oligonucleotide is not an antisense oligonucleotide, triple-helix-forming oligonucleotide, or ribozyme (see abstract, pgs. 2-12, pgs. 18-24, pgs. 27-30, pg. 34, pgs. 36-37).

Art Unit: 1645

Krieg et al teaches that the immunostimulatory nucleic acid may be any size (i. e., length) provided it is at least 4 nucleotides, in important embodiments; the immunostimulatory nucleic acids have a length in the range of between 6 and 100. In still other embodiments, the length is in the range of between 8 and 35 nucleotides. Preferably, the TG oligonucleotides range in size from 15 to 25 nucleotides. Krieg et al teaches the size (i. e., the number of nucleotide residues along the length of the nucleic acid) of the immunostimulatory nucleic acid may also contribute to the stimulatory activity of the nucleic acid. Krieg et al teach that it has been discovered, surprisingly that even for highly immune stimulating immunostimulatory nucleic acids, the length of the nucleic acid influences the extent of immunostimulation that can be achieved and it has been demonstrated that increasing the length of a T-rich nucleic acid up to 24 nucleotides causes increased immune stimulation. Krieg et al teaches that the experiments presented in the examples demonstrate that when the length of the T-rich nucleic acid is increased from 18 to 27 nucleotides the ability of the nucleic acid to stimulate an immune response is increased significantly (compare ODN #2194, 2183, 2195, and 2196 decreasing in size from 27-18 nucleotides). Krieg et al teaches that that increasing the length of the nucleic acid up to 30 nucleotides had a dramatic impact on the biological properties of the nucleic acid but increasing the length beyond 30 nucleotides did not appear to further influence the immune stimulatory effect (e. g., compare ODN 2179 to 2006).

Krieg et al teach that TG nucleic acids ranging in length from 15 to 25 nucleotides in length may exhibit an increased immune stimulation thus, in one aspect, the invention provides an oligonucleotide that is 15-27 nucleotides in length (i. e., an oligonucleotide that is 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26 or 27 nucleotides in length) that may be a T-rich nucleic acid or may be a TG nucleic acid, or may be both a T-rich and a TG nucleic acid. In one embodiment, the oligonucleotide is not a T-rich nucleic acid nor is it a TG nucleic acid. In other embodiments, the oligonucleotide does not have a CG motif. Krieg et al teach that the invention similarly provides oligonucleotides that are 15-27 nucleotides in length, oligonucleotides that are 18-25 nucleotides in

Art Unit: 1645

length, oligonucleotides that are 20-23 nucleotides in length, and oligonucleotides that are 23- 25 nucleotides in length and any of the foregoing embodiments relating to oligonucleotides 15-27 in length also relate to the oligonucleotides of these differing length.

Krieg et al teach that for facilitating uptake into cells immunostimulatory nucleic acids preferably have a minimum length of 6 nucleotide residues. Krieg et al teach that nucleic acids of any size greater than 6 nucleotides (even many kb long) are capable of inducing an immune response according to the invention if sufficient immunostimulatory motifs are present, since larger nucleic acids are degraded inside of cells and preferably the immunostimulatory nucleic acids are in the range of between 8 and 100 and in some embodiments T-rich containing immunostimulatory nucleic acids are between 24 and 40 nucleotides in length and TG containing immunostimulatory nucleic acids are between 15 and 25 nucleotides in length (see abstract, pgs. 2-12, pgs. 18-24, pgs. 27-30, pg. 34, pgs. 36-37).

Krieg et al teaches an oligonucleotide comprising an oligonucleotide comprising: 5'T\*C\_G(N<sub>6</sub>C\_G N<sub>7</sub>)<sub>2-3</sub>T\*C\_G\*T\*T3' wherein N<sub>6</sub> and N<sub>7</sub> are independently between 1 and 5 nucleotides in length, and optionally N<sub>6</sub> is one nucleotide, preferably T or A and optionally N<sub>7</sub> is five nucleotides, preferably five pyrimidines or TTTTG wherein \* refers to the presence of a stabilized internucleotide linkage, and wherein \_ refers to the presence of a phosphodiester internucleotide linkage and wherein the oligonucleotide has a length of 16-40 nucleotides, wherein the oligonucleotide has the following structure: 5' T\*C G\*T\*C G\*T\*T\*T\*T\*G\*A\*C G\*T\*T\*T\*T\*G\*T\*C 'G\*T\*T 3' (SEQ ID NO: 313) (see abstract, pgs. 2-12, pgs. 18-24, pgs. 27-30, pg. 34, pgs. 36-37). STIC Sequence Search Results SEQ ID NO: 331).

***New Grounds***

***Claim Rejection - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-2, 12, 14, 16-17, 22, 24, 26-27, 44, 49, 66-67, 97-98, and 100 under 35 U.S.C. 103(a) as being unpatentable over Krieg et al WO/01/22972A2.

Claims 1-2, 12, 14, 16-17, 22, 24, 26-27, 49, 66-67, 97-98, and 100 are to draw an immunostimulatory nucleic acid molecule having at least one internal pyrimidine-purine (YZ) dinucleotide and a chimeric backbone, wherein the at least one internal YZ dinucleotide has a phosphodiester or phosphodiester-like internucleotide linkage, wherein optionally each additional internal YZ dinucleotide has a phosphodiester, phosphodiester-like, or stabilized internucleotide linkage, and wherein all other internucleotide linkages are stabilized (claim 1); an oligonucleotide comprising an octameric sequence comprising at least one YZ dinucleotide having a phosphodiester or phosphodiester-like internucleotide linkage, and at least 4 T nucleotides, wherein Y is

Art Unit: 1645

a pyrimidine or modified pyrimidine, wherein Z is a guanosine or modified guanosine, and wherein the oligonucleotide includes at least one stabilized internucleotide linkage (claim 49); an oligonucleotide comprising 5'GNC 3', wherein N is a nucleic acid sequence of 4-10 nucleotides in length and is at least 50% T and does not include a CG dinucleotide, and the oligonucleotide includes at least one stabilized internucleotide linkage (claim 67); an oligonucleotide comprising  $N_1-C\_G-N_2-C\_G-N_3$  wherein  $N_1$  and  $N_3$  are each independently a nucleic acid sequence 1-20 nucleotides in length, wherein  $\_$  indicates an internal phosphodiester or phosphodiester-like internucleotide linkage, wherein  $N_2$  is independently a nucleic acid sequence 4-20 nucleotides in length, and wherein  $G-N_2-C$  includes at least 5 stabilized linkages (claim 97); an oligonucleotide comprising  $N_1-C\_G-N_2-C\_G-N_3$  wherein  $N_1$ ,  $N_2$ , and  $N_3$  are each independently a nucleic acid sequence of 0-20 nucleotides in length and wherein  $\_$  indicates an internal phosphodiester or phosphodiester-like internucleotide linkage, wherein the oligonucleotide is not an antisense oligonucleotide, triple-helix-forming oligonucleotide, or ribozyme (claim 98).

Krieg et al teaches an immunostimulatory nucleic acid molecule having at least one internal pyrimidine-purine (YZ) dinucleotide and a chimeric backbone, wherein the at least one internal YZ dinucleotide has a phosphodiester or phosphodiester-like internucleotide linkage, wherein optionally each additional internal YZ dinucleotide has a phosphodiester, phosphodiester-like, or stabilized internucleotide linkage, and wherein all other internucleotide linkages are stabilized, wherein the immunostimulatory nucleic acid comprises a plurality of internal YG dinucleotides having a phosphodiester or phosphodiester-like internucleotide linkage, wherein the at least one internal YG dinucleotide having a phosphodiester or phosphodiester-like internucleotide linkage is CG, wherein the immunostimulatory nucleic acid molecule is a B-Class immunostimulatory nucleic acid molecule, wherein the immunostimulatory nucleic acid molecule is 4-100 nucleotides long, wherein the immunostimulatory nucleic acid molecule is not an antisense oligonucleotide, triple-helix-forming oligonucleotide, or ribozyme, wherein the nucleic acid has a backbone comprising deoxyribose or ribose,

Art Unit: 1645

wherein the phosphodiester or phosphodiester-like internucleotide linkage is phosphodiester, wherein the stabilized internucleotide linkages are selected from the group consisting of: phosphorothioate, phosphorodithioate, methylphosphonate, methylphosphorothioate, and any combination thereof, wherein the stabilized internucleotide linkages are phosphorothioate (see abstract, pgs. 2-12, pgs. 18-24, pgs. 27-30, pg. 34, pgs. 36-37).

Krieg et al teaches an oligonucleotide comprising an octameric sequence comprising at least one YZ dinucleotide having a phosphodiester or phosphodiester-like internucleotide linkage, and at least 4 T nucleotides, wherein Y is a pyrimidine or modified pyrimidine, wherein Z is a guanosine or modified guanosine, and wherein the oligonucleotide includes at least one stabilized internucleotide linkage. Krieg et al teaches an oligonucleotide comprising 5'GNC 3', wherein N is a nucleic acid sequence of 4-10 nucleotides in length and is at least 50% T and does not include a CG dinucleotide, and the oligonucleotide includes at least one stabilized internucleotide linkage. Krieg et al teaches an oligonucleotide comprising  $N_1-C\_G-N_2-C\_G-N_3$  wherein  $N_1$  and  $N_3$  are each independently a nucleic acid sequence 1-20 nucleotides in length, wherein  $\_$  indicates an internal phosphodiester or phosphodiester-like internucleotide linkage, wherein  $N_2$  is independently a nucleic acid sequence 4-20 nucleotides in length, and wherein  $G-N_2-C$  includes at least 5 stabilized linkages. Krieg et al teaches an oligonucleotide comprising  $N_1-C\_G-N_2-C\_G-N_3$  wherein  $N_1$ ,  $N_2$ , and  $N_3$  are each independently a nucleic acid sequence of 0-20 nucleotides in length and wherein  $\_$  indicates an internal phosphodiester or phosphodiester-like internucleotide linkage, wherein the oligonucleotide is not an antisense oligonucleotide, triple-helix-forming oligonucleotide, or ribozyme (see abstract, pgs. 2-12, pgs. 18-24, pgs. 27-30, pg. 34, pgs. 36-37).

Krieg et al teaches that the immunostimulatory nucleic acid may be any size (i.e., length) provided it is at least 4 nucleotides, in important embodiments; the immunostimulatory nucleic acids have a length in the range of between 6 and 100. In still other embodiments, the length is in the range of between 8 and 35 nucleotides.

Art Unit: 1645

Preferably, the TG oligonucleotides range in size from 15 to 25 nucleotides. Krieg et al teaches the size (i. e., the number of nucleotide residues along the length of the nucleic acid) of the immunostimulatory nucleic acid may also contribute to the stimulatory activity of the nucleic acid. Krieg et al teach that it has been discovered, surprisingly that even for highly immune stimulating immunostimulatory nucleic acids, the length of the nucleic acid influences the extent of immunostimulation that can be achieved and it has been demonstrated that increasing the length of a T-rich nucleic acid up to 24 nucleotides causes increased immune stimulation. Krieg et al teaches that the experiments presented in the examples demonstrate that when the length of the T-rich nucleic acid is increased from 18 to 27 nucleotides the ability of the nucleic acid to stimulate an immune response is increased significantly (compare ODN #2194, 2183, 2195, and 2196 decreasing in size from 27-18 nucleotides). Krieg et al teaches that that increasing the length of the nucleic acid up to 30 nucleotides had a dramatic impact on the biological properties of the nucleic acid but increasing the length beyond 30 nucleotides did not appear to further influence the immune stimulatory effect (e. g., compare ODN 2179 to 2006).

Krieg et al teach that TG nucleic acids ranging in length from 15 to 25 nucleotides in length may exhibit an increased immune stimulation thus, in one aspect, the invention provides an oligonucleotide that is 15-27 nucleotides in length (i. e., an oligonucleotide that is 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26 or 27 nucleotides in length) that may be a T-rich nucleic acid or may be a TG nucleic acid, or may be both a T-rich and a TG nucleic acid. In one embodiment, the oligonucleotide is not a T-rich nucleic acid nor is it a TG nucleic acid. In other embodiments, the oligonucleotide does not have a CG motif. Krieg et al teach that the invention similarly provides oligonucleotides that are 15-27 nucleotides in length, oligonucleotides that are 18-25 nucleotides in length, oligonucleotides that are 20-23 nucleotides in length, and oligonucleotides that are 23- 25 nucleotides in length and any of the foregoing embodiments relating to oligonucleotides 15-27 in length also relate to the oligonucleotides of these differing length.



Art Unit: 1645

Krieg et al teach that for facilitating uptake into cells immunostimulatory nucleic acids preferably have a minimum length of 6 nucleotide residues. Krieg et al teach that nucleic acids of any size greater than 6 nucleotides (even many kb long) are capable of inducing an immune response according to the invention if sufficient immunostimulatory motifs are present, since larger nucleic acids are degraded inside of cells and preferably the immunostimulatory nucleic acids are in the range of between 8 and 100 and in some embodiments T-rich containing immunostimulatory nucleic acids are between 24 and 40 nucleotides in length and TG containing immunostimulatory nucleic acids are between 15 and 25 nucleotides in length (see abstract, pgs. 2-12, pgs. 18-24, pgs. 27-30, pg. 34, pgs. 36-37).

Krieg et al teaches an oligonucleotide comprising an oligonucleotide comprising: 5'T\*C\_G(N<sub>6</sub>C\_G N<sub>7</sub>)<sub>2-3</sub>T\*C\_G\*T\*T3' wherein N<sub>6</sub> and N<sub>7</sub> are independently between 1 and 5 nucleotides in length, and optionally N<sub>6</sub> is one nucleotide, preferably T or A and optionally N<sub>7</sub> is five nucleotides, preferably five pyrimidines or TTTTG wherein \* refers to the presence of a stabilized internucleotide linkage, and wherein \_ refers to the presence of a phosphodiester internucleotide linkage and wherein the oligonucleotide has a length of 16-40 nucleotides, wherein the oligonucleotide has the following structure: 5' T\*C G\*T\*C G\*T\*T\*T\*T\*G\*A\*C G\*T\*T\*T\*T\*G\*T\*C 'G\*T\*T 3' (SEQ ID NO: 313) (see abstract, pgs. 2-12, pgs. 18-24, pgs. 27-30, pg. 34, pgs. 36-37). STIC Sequence Search Results SEQ ID NO: 331).

Although Krieg et al is silent to the teaching of an internal YG dinucleotide having a phosphodiester or phosphodiester-like internucleotide linkage.

Krieg et al teach phosphodiester or phosphodiester-like internucleotide linkage, for the purpose of nucleic acid It has been demonstrated that modification of the nucleic acid backbone provides enhanced activity. Krieg et al teach modified nucleic acids may show more stimulatory activity due to enhanced nuclease resistance, increased cellular uptake, increased protein binding, and/or altered intracellular localization.

It would have been prima facie obvious at the time the invention was made to incorporate phosphodiester or phosphodiester-like internucleotide linkage as taught by

Art Unit: 1645

Krieg et al in YG dinucleotide as taught by Krieg et al because Krieg et al teach Krieg et al teach modified nucleic acids may show more stimulatory activity due to enhanced nuclease resistance, increased cellular uptake, increased protein binding, and/or altered intracellular localization.

### ***Status of the Claims***

6. No claims are allowed.

Claims 1-2, 12, 14, 16-17, 22, 24, 26-27, 44, 49, 66-67, 97-98, and 100 are rejected.

### ***Conclusion***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should

Art Unit: 1645

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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